REMARKS/ARGUMENTS

With this amendment, claims 1-6, 14-16, and 19 are pending. For convenience, the Examiner's rejections are addressed in the order presented in the January 8, 2003 Office Action.

I. Status of the claims

Claim 1 is amended to read "a nucleic acid that hybridizes under stringent conditions to a complement of a nucleic acid" that encodes an ILKAP protein. Support for this amendment is found throughout the specification, for example at page 4, lines 30-31. This amendment is merely cosmetic and is not a narrowing amendment. This amendment adds no new matter.

Claim 1 is amended to recite that the ILKAP protein has an anti-angiogenic phenotype. Support for this amendment is found throughout the specification, for example at page 3, lines 29-34; page 29, lines 3-10, and Example 1, page 44-45. This amendment is merely cosmetic and is not a narrowing amendment. This amendment add no new matter.

Claim 1 is amended to recite specific stringent hybridization conditions. Support for this amendment is found throughout the specification, for example at page 13, lines 3-5. This amendment is merely cosmetic and is not a narrowing amendment. This amendment adds no new matter.

Claim 1 is amended to recite that a difference in functional effect without the compound indicates that the compound modulates angiogenesis. Support for this amendment is found throughout the specification, for example at page 6, lines 23-25. This amendment is merely cosmetic and is not a narrowing amendment. This amendment adds no new matter.

II. Rejections under 35 U.S.C. §112, second paragraph

Claims 1-6, 14-16, and 19 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. To the extent the rejections apply to the claims as amended, Applicants respectfully traverse the rejections.

Claim 1 is rejected for failing to recite specific hybridization conditions. At the suggestion of the Examiner, Applicants have amended claim 1 to include the following stringent hybridization conditions: 50% formamide, 5x SSC, and 1% SDS, incubating at 42°C; or 5x SSC, 1% SDS, incubating at 65°C, with wash in 0.2x SSC, and 0.1% SDS at 65°C.

Claim 1 is also rejected for allegedly reading on an antisense nucleic acid sequences that does not encode the ILKAP protein. In order to expedite prosecution, Applicants have amended claim 1 to recite "a nucleic acid that hybridizes under stringent conditions to a complement of a nucleic acid" that encodes an ILKAP protein.

Claim 1 is also rejected for allegedly omitting an essential step of determining the affect of a compound on inhibition of angiogenesis. In order to expedite prosecution, Applicants have amended claim 1 to include a step of comparison of anti-angiogenesis phenotype in the absence of the compound.

In view of the above amendments and remarks, Applicants respectfully request the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

III. Rejections under 35 U.S.C. §112, first paragraph, enablement

1. Introduction

Claims 1-6, 14-16, and 19 are rejected as allegedly claiming subject matter that is not enabled by the specification. As a first matter, the Office Action alleges that the claimed nucleic acids do not encode an ILKAP protein. In order to expedite prosecution, Applicants have amended claim 1 to read on nucleic acids that hybridize under stringent conditions to the complement of a nucleic acid that encodes the ILKAP protein.

The Office Action states that nucleic acids encoding polypeptide variants are not enabled. Furthermore, the Examiner is apparently concerned about inoperable embodiments. *See, e.g.,* Office Action, page 4. As amended, the claims now read on ILKAP polypeptides that have an anti-angiogenic phenotype. *See, e.g.*, page 3, lines 29-34.

As identified in the Patent Office and the Federal Circuit, whether undue experimentation is required by one skilled in the art to practice an invention is determined by considering factors such as the amount of guidance presented in the application, the state of the

prior art, and the presence of working examples. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985); *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, a "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should precede." *Wands*, 8 USPQ2d at 1404 (quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982).

The claimed methods now specify hybridization conditions, as well as reference sequences to which the claimed nucleic acids must hybridize. Hybridization methods for the identification of nucleic acids are also are well known to those of skill in molecular biology. These elements therefore provide adequate guidance for routine identification of the nucleic acids of the invention. In addition, claimed functional characteristics of the proteins encoded by the claimed nucleic acids would allow one of skill in the art to identify operable embodiments and exclude inoperable embodiments. Finally, Applicants clearly meet the PTO guidelines for enablement, which set forth the standard for the scope of enablement when a large number of possible embodiments exists. Thus, undue experimentation is not required to practice the claimed invention.

2. The claimed reference sequences provide a meaningful structural feature that allows one of skill to identify the claimed sequences without undue experimentation.

The rejection alleges that the specification provides enablement only for identification of compounds that modulate angiogenesis using a nucleic acid encoding an ILKAP polypeptide comprising an amino acid sequence of SEQ ID NO:2 or for a nucleic acid that hybridizes under stringent conditions to the full length of a nucleic acid that encodes SEQ ID NO:2. However, the claims now recite both functional and structural characteristics of the ILKAP nucleic acids of the invention. The present application also provides functional assays for identification of nucleic acids encoding ILKAP polypeptides of the invention, without undue experimentation. The assays and examples of the specification, together with standard methodology known to those of skill in the art, therefore provide adequate guidance for identifying claimed nucleic acids that encode the ILKAP polypeptides of the invention.

The assertion of undue experimentation appears to be based on an assumption that enablement requires the description of each and every nucleic acid that could be used in the claimed methods. As noted below, such a requirement is not consistent with the patent laws. Indeed, it is well settled in the biotechnology art that routine screening of even large numbers of samples is not undue experimentation when a probability of success exists. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Using the conditions set forth in the claims and specification and routine methodology, any competent laboratory technician in a molecular biology laboratory could isolate and prepare appropriate constructs, transform cells, and identify those nucleic acids that encode an ILKAP protein of the invention. As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments." In the present case, one of skill, given the reference amino acid and nucleotide sequences and the specified hybridization conditions, could easily screen for other nucleic acid and protein molecules that can be used in the claimed methods.

The present invention describes a method of identifying compounds that modulate angiogenesis using a family of nucleic acids encoding polypeptides which functionally are ILKAP polypeptides and which structurally hybridize to nucleic acids that encode a reference polypeptide.

At the time of the present invention, identification of nucleic acids having the functional and structural characteristics described above was well within the means of one of skill of the art, without undue experimentation. The present specification provides working examples and discloses standard techniques known to those of skill in the art, for the identification of functional ILKAP polypeptides such as that exemplified by SEQ ID NO:2 (*see, e.g.*, specification at page 12, line 22 through page 13, line 17).

Finally, functional assays to identify ILKAP polypeptides (*i.e.*, with anti-angiogenic phenotypes) of the invention are known to those of skill in the art and are disclosed in the specification. For example, the specification describes methods of determining an effect on angiogenesis through disclosure of multiple angiogenesis assays. Assays for angiogenesis include assays for expression of cell surface markers, such as $\alpha v\beta 3$ (page 3, page 5, page 17, and exemplified in Example 1 at pages 44-45); haptotaxis assays (page 3, page 5, page 17, and

exemplified in Example 1 at page 45); a chick CAM assay (pages 5 and 29); a mouse corneal assay (pages 5 and 29); and assays for neovascularization of tumors (pages 6 and 29).

The assays described in the specification, coupled with methodology well known to those of skill in the art, therefore demonstrate that screening for nucleic acids which encode ILKAP polypeptides having the structural and functional characteristics described above is routine. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Applicants therefore respectfully request that the rejection be withdrawn.

3. One of skill in the art could readily determine any one of the claimed nucleic acids.

Regarding the issue of enablement for nucleic acids, where a large number of possible embodiments exist, the PTO has provided express guidelines for examination. As set forth in the MPEP § 2164.08, a rejection of claims such as those in the present application for undue breadth is inappropriate where one of skill could readily determine any one of the claimed embodiments.

This standard is further explained in the "Training Materials for Examining Patent Applications with respect to 35 U.S.C. § 112, first paragraph – Enablement Chemical/Biotechnological Applications," section III.A.2.b.i(c). In the guidelines, the PTO specifically answers the question regarding scope of a nucleic acid composition claim (e.g., in the present case, a nucleic acid encoding a ILKAP protein) left open by the Federal Circuit in *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995). The claims at issue in *Deuel* were directed to any DNA encoding a specific amino acid sequence. Thus, a great number of nucleic acids were within the scope of the claims. In fact, the number was so great that a listing of all possible DNAs encoding the protein was a practical impossibility.

In the guidelines, the PTO addressed this issue, explaining that "even though a listing of all possible DNAs which encode a given protein is a practical impossibility due to the enormous number of such nucleic acids, any particular sequence can be written by one of skill given the disclosure and the sequence can be ordered from a company which synthesizes DNA." In this manner, one of skill in the art can readily determine any one of the embodiments. The

PTO concluded that scope rejections such as the one hypothesized in *Deuel* should not be advanced.

In the present application, one of skill in the art has only to identify nucleic acids that hybridize under specified conditions to nucleic acids that encode the conserved reference amino acid sequence of SEQ ID NO:2, using techniques described in the specification or known to those of skill in the art. Although many such nucleic acids are possible, one of skill can readily determine, one by one, any particular ILKAP encoding nucleic acid, without undue experimentation. For example, nucleic acid screening, hybridization, and PCR techniques are described in the specification and the art, as described above. Furthermore, one of skill can use the assays described above to test the functionality of the protein encoded by the nucleic acid of interest and easily determine if it falls within the scope of the claims. Thus, in the present application the skilled artisan can readily, with only routine experimentation, make and test any particular ILKAP encoding nucleic acid.

The specification, combined with the state of the prior art, thus provides a number of different assays demonstrating that any experimentation required to identify nucleic acids encoding ILKAP proteins is not undue. *In re Wands*, 8 USPQ 1400 (Fed. Cir. 1988). Applicants respectfully request that the rejection be withdrawn.

4. Use of the term comprising does not require undue experimentation to practice the claimed invention.

The Office Action also rejects the claims because claim 1 uses the phrase "comprising an amino acid sequence of SEQ ID NO:2". According to the Office Action, the term comprising is open ended and its use would require undue experimentation by one of skill in the art to practice the claimed invention. Applicants respectfully traverse.

Addition of amino acids to the C-terminus or N-terminus of a recombinant protein is well-known to those of skill in the art. For example, epitope tags are frequently added to recombinant proteins to assist in isolation or detection of the recombinant protein. (See, *e.g.*, page 21, lines 14-15 and page 28, lines 27-30.) The claims as written require a genus of nucleic acids that encode an ILKAP protein that has an anti-angiogenic phenotype. Given the

knowledge of one of skill in the art and the disclosure of the specification, undue experimentation is not required to practice the claimed invention and the scope of the claims correlates with the protection sought by Applicants.

In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, enablement be withdrawn.

IV. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 1, 2, and 12 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification as originally filed. In the Office Action the Examiner observed that the purpose of the written description requirement is to convey to one skilled in the relevant art that the inventors had possession of the claimed invention as of the filing date. The Examiner went on to state that "[T]he skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the claims." Office action at page 5.

To the extent that the rejection applies to the claims as amended, Applicants respectfully traverse. The application fully complies with the requirements for written description of a chemical genus as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). Quoting *Fiers v. Revel* the court stated that an adequate written description for a chemical genus "requires a precise definition, such as by structure, formula, chemical name, or physical properties." (See Lilly at 1405, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993)). As described by the Federal Circuit in *Lilly*, "[a] description of a genus of cDNAs may be achieved by "recitation of a representative number of [species]. . . **or** a recitation of structural features common to the members of the genus . . ." *Lilly*, 43 USPQ2d at 1406 (emphasis added).

As described above, the present invention is a method for identifying modulators of angiogenesis using ILKAP polypeptides. The genus of ILKAP nucleic acids and the proteins that they encode is claimed by reference to shared structural features, *i.e.*, nucleic acid sequences (SEQ ID NO:1) that encode the entire ILKAP protein (SEQ ID NO: 2). The claims also provide

hybridization conditions in which the claimed genus of ILKAP nucleic acids hybridize to nucleic acids that encode the reference sequences.

The ability of a particular nucleic acid to hybridize under *given conditions* to a reference nucleic acid is a physical/structural property of the nucleic acid, because it relies upon the nucleotide sequence of the molecule (*see, e.g.*, Sambrook, *Molecular Cloning: A Laboratory Manual*, pp. 9.47-9.51 (2nd ed. 1989); *see also* Stryer, *Biochemistry*, pp. 573 (2nd ed. 1975)). As described in Stryer, the transition between hybridization and melting of complementary nucleic acid strands is abrupt and largely sequence dependent. When the temperature of hybridization is provided, one of skill in the art would be able to predict whether or not a given sequence would hybridize to a reference sequence (*see, e.g.*, equations provided in Sambrook, *supra*).

In the present application, Applicants have provided both reference amino acid sequences, and nucleotide sequences, as well as hybridization conditions. As required by the standard set forth in *University of California v. Eli Lilly*, these structural features are common to all of the members of the ILKAP polypeptide genus. The sequences encoding structural features of the genus, and the given conditions under which the claimed genus would hybridize to such reference sequences or have a specified identity to such sequences "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (*see*, Office Action, page 4, *quoting Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 111, 1116 (Fed. Cir. 1991)). The specification thus appropriately describes the claimed ILKAP nucleic acid and protein genus using structural/physical features, as required by the court in *University of California v. Eli Lilly*. As such, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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